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Is Precision Treatment Possible for Depression?

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Depression, a leading cause of disability worldwide, can be successfully treated by several evidence-based interventions. However, individual responses to these treatments vary significantly, and many individuals undergo multiple therapies before finding what works best for them. Precision treatment for depression aims to address these challenges by identifying effective treatments based on individual characteristics. In doing so, precision treatment has the potential to reduce trial-and-error prescribing, shorten the time to remission, and lower the global burden of depression. However, despite decades of research, precision treatment has yet to be fully realized for depression, and its clinical utility remains limited. This article provides examples of recent and relevant attempts at identifying predictors of differential treatment response and raises some methodological, conceptual, and practical concerns of implementing precision treatment for depression. Future directions and clinical implications for advancing personalized approaches to depression treatment are also discussed.

Public Significance Statement
Precision treatment for depression has the potential to transform mental health care by matching individuals to the most effective treatments based on their unique characteristics. However, significant practical and conceptual challenges have delayed its widespread application. Continued research and a focused effort to address these barriers are essential for precision treatment for depression to become a reality in clinical practice.

Keywords: precision medicine, precision psychiatry, personalized medicine, personalized treatment, depression

For decades, psychotherapy researchers have asked a central question: "What treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances?" (Paul, 1967, p. 111). This question is particularly pressing for depression, a leading cause of disability worldwide (World Health Organization, 2023). Depression can be successfully treated by several evidence-based psychological approaches, including cognitive-behavioural therapy (CBT), behavioural activation (BA), and interpersonal psychotherapy (IPT), as well as pharmacotherapies such as selective serotonin reuptake inhibitors (SSRIs; Cuijpers et al., 2025; Westen & Morrison, 2001). However, individual responses to these treatments vary significantly (Simon & Perlis, 2010), and many patients do not improve with their first course of therapy (Hollon et al., 2002). Precision treatment—the selection of treatment based on individual biological, psychological, and environmental characteristics (President's Council of Advisors on Science and Technology, 2008)—offers a theoretical solution to improve outcomes for individuals with depression. By identifying a priori which treatment an individual will respond best to, precision treatment could reduce reliance on trial-and-error prescribing, shorten the time to remission, and lower the global burden of depression. Despite its promise, the practical and scientific feasibility of precision treatment for depression is fraught with significant challenges, making it an ambitious but currently limited paradigm.

This article highlights the promises, challenges, and future directions of precision treatment for depression. First, examples of recent and relevant attempts to identify factors thought to predict differential responses between treatment types (e.g., psychotherapies vs. pharmacotherapies) for depression are explored. Second, various limitations that continue to dampen the implementation of precision treatment for depression (e.g., inconsistencies in the evidence, practical feasibility, measurement challenges, neglect of the sociocultural context, conceptual issues) are discussed. Finally, future directions and implications for both researchers and clinicians are advanced, identifying what can be done currently and what should be accomplished in the future, to advance precision treatment for depression.

The Promise of Precision Treatment for Depression

Precision treatment has been successfully applied across medical fields, such as in cancer patients, to identify predictors of treatment

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response (Hoeben et al., 2021). Decades ago, psychotherapy researchers defined Aptitude × Treatment interactions (Cronbach & Snow, 1977) and examined how individual differences moderate the effectiveness of different therapeutic interventions. Termed "precision psychiatry," researchers are now interested in enhancing the treatment of psychiatric disorders by identifying subgroups that will benefit from specific therapies (Fernandes et al., 2017). Theoretically, precision treatment may be especially relevant to depression due to its heterogeneous and multifactorial nature (Athira et al., 2020). As Ingram et al. (1998) argued, two people with depression can differ on virtually every symptom, etiology, presentation, and course but have the same diagnosis of depression. For example, in a sample of 3,703 patients with depression, Fried and Nesse (2015) identified 1,030 unique symptom profiles; such individual variations in depressive symptoms may be uniquely related to treatment response. Depression cannot be understood as a homogeneous condition that affects everyone in the same way and responds uniformly to treatment. Instead, depression is best characterized as a heterogeneous condition, warranting a personalized treatment approach.

Indeed, although different therapies tend to be equally effective for depression *on average* (Cuijpers et al., 2011), individual responses to treatment are highly variable (Simon & Perlis, 2010). Cuijpers (2017) argued that more than 40% of patients only partially respond to treatment if at all, and less than one third recover completely following treatment (Ormel et al., 2022). Given that many patients who seek help for their depression do not respond to treatment initially (Cuijpers et al., 2014; Harkness, 2023; Hollon et al., 2002), they may go through multiple therapies before finding what works best for them (Rush et al., 2006). Patients who do not respond to two or more classes of antidepressants are considered to have treatment-resistant depression (Gelenberg et al., 2010; Kennedy et al., 2016), and these individuals, in particular, would benefit from a personalized approach. It is promising, however, that some patients who do not respond to one treatment initially will experience a strong response when switched to an alternative approach (Dunlop, 2016; Schatzberg et al., 2005). Therefore, there must be individual differences in treatment response that, once identified, can be used to improve the precision of treatment selection.

Unfortunately, there is currently no way to predict which patients with depression will benefit from which treatments, making it necessary to use a trial-and-error approach or rely on clinical judgement (Warden et al., 2007). Although using clinical judgement to select appropriate treatments is an *intuitive* approach to personalized treatment, this method is plagued by biases and usually outperformed by data-driven, actuarial approaches (Cohen et al., 2021; Grove & Meehl, 1996; Meehl, 1954). This current clinical prediction approach to treatment selection is problematic; patients matched with the "wrong" treatment may be more likely to discontinue treatment prematurely; experience relapse, recurrence, or delayed remission; or assume that therapy "does not work for them," thereby reducing future help-seeking behaviours and contributing to the global burden of depression. Indeed, after receiving initial treatment with antidepressants, only half of patients with depression attend follow-up appointments, and only a quarter pursue additional treatment options (Simon et al., 2011). Precision treatment may resolve these challenges by guiding treatment selection based on individual characteristics. By focusing on what works best for whom, precision treatment moves beyond average treatment effects and holds promise for improving depression treatment.

Recent Attempts at Precision Treatment for Depression

To optimize treatment selection, individual characteristics that reliably predict differential treatment outcomes (i.e., better response to one therapy relative to another), often referred to as "moderators" or "prescriptive variables," must be identified. A large body of research has aimed to identify factors that predict differential responses to psychotherapies and pharmacotherapies for depression. Other attempts have been made to identify predictors of response to specific treatments for depression (see Nogovitsyn et al., 2020; Saeedi et al., 2021; Zhdanov et al., 2020). Despite significant effort, however, no single moderator has been identified as sufficiently robust to reliably guide treatment selection for depression (Cohen & DeRubeis, 2018; Kessler, 2018; Simon & Perlis, 2010). Recent advances have shifted toward using multivariate prediction models that examine the combined effect of multiple moderators (Cohen & DeRubeis, 2018; Cohen et al., 2021), though their clinical utility remains limited. Although some evidence supports potential predictors of differential treatment response, current findings are inconsistent and in need of replication, leading to uncertainty about the near feasibility of precision treatment for optimizing depression treatment.

Biological Markers of Differential Treatment Response for Depression

A significant focus has been placed on identifying genetic, inflammatory, neuroendocrine, neurological, and other biological markers that could predict differential responses to treatments for depression. Salagre and Vieta (2021) went so far as to argue that "precision psychiatry will eventually deliver because there is no question, in our opinion, that mental disorders are disorders of the brain" (p. 1413). Despite advances in pharmacogenetics, genomics, proteomics, metabolomics, neuroimaging, and neuroendocrinology, no findings have led to effective precision treatments for depression (Cuijpers, 2017).

One leading step in developing personalized approaches has involved identifying genetic markers that predict response to pharmacotherapy (Gómez-Carrillo et al., 2023). However, attempts to identify genes associated with differential treatment response for depression are limited because no single gene or group of genes can explain depression (Lohoff, 2010). A recent genome-wide association meta-analysis of over one million individuals, including 371,184 participants with depression, identified 243 loci associated with depression risk (Als et al., 2023). Researchers found that depression was extremely polygenic, with over 11,000 variants explaining 90% of its heritability. Notwithstanding the polygenic nature of depression, pharmacogenomics holds promise for precision treatment for depression by recognizing that an individual's unique genetic code influences their metabolism of, and thus their response to, medication. Overall, modest effects have been found for pharmacogenomic-guided care (i.e., recommendations for antidepressant treatment based on individuals' unique genetic profiles) compared to treatment as usual in improving response and remission during antidepressant treatment in adults with moderate-to-severe depression (Brown et al., 2022; Bunka et al., 2023).

Notwithstanding these findings, the evidence base used to draw these conclusions is plagued with a high risk of bias and inconsistent findings (Bunka et al., 2023). Relatedly, therapygenetics aims to understand how genetic variation impacts outcomes in psychotherapy. However, a genome-wide association meta-analysis of individuals receiving CBT for anxiety and depressive disorders failed to find any strong genetic predictors of therapy outcome (Rayner et al., 2019).

Clearly, current evidence suggests that genetic factors, on their own, are not sufficient to determine differential treatment response for depression. Instead, environmental factors may interact with genetic vulnerabilities to determine treatment response (e.g., a diathesis-stress model). For example, individuals at high genetic risk for depression are more likely to develop treatment-resistant depression when they also experience a stressful life event (Mitchell et al., 2024). Through a process known as epigenetics, environmental stressors, such as early life trauma, can alter gene expression, giving rise to depression in individuals who have an underlying genetic vulnerability (Klengel & Binder, 2015). Thus, an understanding of the role of genetics in determining differential treatment response for depression may be incomplete without acknowledging gene–environment interactions.

Findings from neuroimaging studies have demonstrated some promise in guiding treatment selection for different depression subtypes. For instance, brain activation patterns such as higher pretreatment activation of the anterior cingulate cortex, lower baseline responsivity in limbic regions, and increased dorsal prefrontal responses to emotional stimuli are significant predictors of response to pharmacological treatment for depression (Ball et al., 2014; Seeberg et al., 2018). Tozzi et al. (2024) recently used functional magnetic resonance imaging to identify subgroups that may benefit more from either pharmacotherapy or behaviour therapy for depression. Participants were classified into six "biotypes" determined by distinct profiles of activation and functional connectivity between brain regions implicated in depression. These biotypes were distinguished by their symptoms, behavioural performance on emotional and cognitive tasks, and, importantly, treatment response. Researchers identified specific biotypes that would benefit most from behaviour therapy and those that would benefit most from antidepressants. Therefore, neuroimaging has the potential to inform precision treatment for depression in the future, but supportive research is in its infancy.

The Canadian Biomarker Integration Network in Depression—Canada's largest depression research network—represents a group of researchers dedicated to leveraging biomarker research to identify which treatments work best for whom. Schwartzmann et al. (2023) recently found that noninvasive brain imaging using electroencephalography was modestly accurate in predicting differential response between two SSRIs. In another electroencephalography study, Dhami et al. (2023) found that a brain signal indicating stronger impulse control predicted better treatment outcomes; however, this signal could not differentiate responsivity to SSRIs versus CBT. Using functional magnetic resonance imaging, Dunlop et al. (2017) found that differences in functional connectivity between brain regions predicted differential response to antidepressant versus CBT. Specifically, negative scores of functional connectivity between certain brain regions were associated with remission following medication but treatment failure with CBT whereas positive scores of functional connectivity showed the opposite effect. Although the concerted effort from Canadian researchers in identifying biomarkers of differential treatment response shows promise, many findings have yet to be replicated or implemented into clinical practice.

In general, the biological markers thought to lead the way to precision treatment for depression have had little impact on clinical practice (Loth et al., 2021). To date, no genetic, neurological, or biological markers of differential responses to treatment for depression have demonstrated the sensitivity or specificity necessary to make them clinically useful. Furthermore, as Gómez-Carrillo et al. (2023) argued, the investigation of biomarkers for precision treatment may be inherently limited because it neglects the broader social context that can also influence treatment outcomes. For example, in a randomized controlled trial of 665 adults with depression, socioeconomic factors such as low education, unemployment, or ethnic minority status were associated with a lesser response to antidepressant medication (Mills et al., 2022). Thus, biomarkers are unlikely to be the sole predictor of differential treatment response.

Clinical and Demographic Moderators of Treatment Response for Depression

Research into clinical and demographic characteristics as moderators of treatment response for depression has yielded mixed results, with no consistent moderators identified across studies. This mirrors the challenges faced in genetic, neurological, and other biomarker research, where conflicting findings complicate efforts to identify reliable predictors for precision treatment. Even large meta-analyses, reviewing multiple potential moderators, have identified only a few variables that appear to have any significant impact on treatment outcomes (Cuijpers et al., 2016). This is particularly disappointing given that the notion that actuarial prediction outperforms clinical prediction has been recognized for decades (Meehl, 1954). Clearly, clinical outcomes can improve by consulting empirical evidence, but the lack of data supporting robust and reliable moderators of treatment response leaves clinicians largely reliant on biased judgement.

The role of personality disorders in moderating treatment response has been particularly inconsistent. Two studies found that the presence of a personality disorder or maladaptive personality traits predicts better response to SSRIs than to CBT (Bagby et al., 2008; Fournier et al., 2009), but another study found no such effect (Maddux et al., 2009). Conversely, some research suggests that comorbid personality disorders are associated with a greater benefit from pharmacotherapy when combined with psychotherapies such as IPT or brief psychodynamic therapy, than pharmacotherapy alone (Bellino et al., 2006; Kool et al., 2003). In contrast, other studies indicate that certain personality characteristics, such as borderline or avoidant traits, predict better outcomes from cognitive therapy (CT) than IPT (Barber & Muenz, 1996; Joyce et al., 2007; McBride et al., 2006). Disagreements in the literature highlight the complexity of using single personality disorders or traits as moderators of treatment response.

The impact of childhood maltreatment on differential treatment response has also generated mixed findings. Among patients with chronic depression, a history of childhood maltreatment predicted better response to psychotherapy compared to nefazodone, an antidepressant (Nemeroff et al., 2003). Harkness et al. (2012) found that individuals with a history of childhood trauma had lower

response rates to IPT than CBT or antidepressants, but this effect was not sustained at 12-month follow-up. A recent meta-analysis of 29 studies with 6,830 participants with depression found no significant moderating effect of early life stress on response to different types of psychotherapies, medications, or their combination (Kuzminskaite et al., 2022). However, the meta-analysis treated early life stress as a binary variable and did not consider its dimensional features. Specific features of early life stress may be differentially related to treatment response. Goerigk et al. (2024), for example, found that more complex and severe maltreatment, including combinations of emotional neglect, emotional abuse, and physical abuse, predicted better response to cognitive behavioural analysis system of psychotherapy (McCullough, 2000) than to nonspecific psychotherapy. Therefore, how potential moderators are conceptualized and measured may also contribute to inconsistencies within the literature.

Further research has explored additional clinical and demographic variables as potential moderators. In a systematic review and meta-analysis, Cuijpers et al. (2016) examined randomized trials that compared outcomes between psychotherapies with a specific characteristic. Across 41 studies, 27 characteristics of patients were examined, but only three—being of older age, having a comorbid addictive disorder, and being a university student—significantly moderated treatment outcomes (i.e., predicted better outcomes in CBT relative to its comparison). One study found that the presence of recent life stress, unemployment, and being married or living with a partner predicted more favourable outcomes with CT than paroxetine, an SSRI (Fournier et al., 2009). Another study examined whether negative unrealistic cognitions and interpersonal relationship difficulties predict differential responses to CBT or combined CBT with antidepressant medication among 431 depressed adolescents (Gunlicks-Stoessel et al., 2019). Latent class analyses identified three subgroups (i.e., those low, moderate, or high in both domains), but these subgroups did not predict treatment outcomes with CBT or combined CBT with SSRIs. Overall, *some* clinical and demographic characteristics are associated with differential treatment response, but no consistent and robust moderators have been identified.

Personalized Advantage Index

A specific example of precision treatment for depression is DeRubeis et al.'s (2014) Personalized Advantage Index (PAI), a model designed to predict the optimal treatment for an individual based on pretreatment characteristics. Not only does the PAI identify which treatment is most likely to benefit a patient, but it also estimates the magnitude of that advantage. To assess the utility of the PAI, researchers can compare outcomes between patients who are randomly assigned to their indicated treatment (based on their PAI) and those assigned to a nonindicated treatment. Although the PAI represents a significant attempt at precision treatment for depression and has been supported by multiple trials, it has failed to make an impact in clinical settings.

One key trial tested the PAI by comparing antidepressant medications and CBT using the Hamilton Rating Scale for Depression (Hamilton, 1960) to measure changes in depressive symptoms (DeRubeis et al., 2014). Results showed significantly better outcomes when patients were assigned to their optimal treatment, based on the PAI, than a nonoptimal treatment. The PAI was calculated using five prerandomization variables: marital status, employment status, life events, comorbid personality disorder, and prior medication trials. The five variables used in the PAI were identified as prescriptive, meaning they predicted differential treatment outcomes based on the treatment chosen. Specifically, comorbid personality disorder favoured antidepressant medication, whereas being married or cohabitating, experiencing a greater number of stressful life events, going through more prior antidepressant trials, and being employed or expected to work all predicted better response to CBT (note, however, that Fournier et al.'s, 2009, study found that *unemployment* predicted greater response to CBT relative to SSRIs). Notably, for 60% of participants, a clinically meaningful advantage was predicted for one treatment, relative to the other. This finding suggests that, although a specific treatment may be more effective for many individuals, there is a subset of patients who will experience similar benefits from either treatment. DeRubeis et al. (2014) suggested that, for the latter group, factors such as patient preference or treatment costs should also be weighed heavily in the decision between treatments. Indeed, patient preference is an important factor in treatment outcomes, with a preference for psychotherapy or pharmacotherapy strongly predicting a better response to the preferred treatment (Nemeroff et al., 2003).

Building on the initial study, van Bronswijk et al. (2021) sought to extend the PAI model by investigating its application to long-term depression outcomes following acute psychotherapy—either CT or IPT. These researchers found a small advantage when participants were assigned to their optimal treatment relative to their nonoptimal treatment and a subgroup of participants exhibited a significant advantage in CT. Furthermore, factors such as an increase in the number of life events prior to treatment and traumatic childhood experiences were associated with higher follow-up depressive severity in IPT compared to CT.

Overall, the PAI represents a promising step toward precision treatment for depression. The findings suggest that precision treatment *can* lead to better outcomes for a majority of patients, but the benefits are not universal. Although PAI-based treatment assignments showed significant advantages for many, other factors like patient preference and treatment costs must also be considered in clinical decisions. However, more research may be required to refine this model and determine exactly how it can be integrated into clinical practice.

Limitations of Precision Treatment for Depression

Although precision treatment demonstrates promise in treating depression, its application is currently limited by inconsistent evidence and significant practical and conceptual challenges. The complexity of depression itself suggests that a fully personalized approach to treatment may not be achievable in the near future. Limitations slowing the realization of precision treatment for depression include concerns about practical feasibility, the measurement of potential moderators, failure to consider the sociocultural context, and conceptual challenges.

Practical Limitations

One major barrier to implementing precision treatment for depression is that the approach requires a significant amount of money and resources. Indeed, Kessler (2018) argued that cost-effectiveness and feasibility should be a necessary consideration in study designs testing personalized approaches. Advanced technology, such as neuroimaging and genetic testing, are often integral to identifying

biomarkers or moderators of treatment response but are neither accessible nor affordable. Besides the costs of advanced technology itself, there are considerable expenses associated with training clinicians in different aspects of precision treatment. For example, training in pharmacogenomics or machine learning may be necessary for clinicians to make use of and interpret data. However, this training is not widely accessible, and clinicians' skepticism of data-driven approaches may serve as another significant barrier to precision treatment implementation (Deisenhofer et al., 2024). Additionally, large data sets that may inform precision treatment in the future require expensive computational systems that clinicians in smaller practices may not have access to (Cirillo & Valencia, 2019; Deisenhofer et al., 2024). Thus, the costs and resources required to identify biomarkers may hinder their use in clinical practice. Importantly, these costs will disproportionately affect low-income countries, meaning that inequities between patients could determine who can and cannot access personalized health services, further contributing to health disparities (Hekler et al., 2020).

Measurement Challenges

How potential moderators of treatment response are measured also limits the applicability of precision treatment. Most studies measure potential moderators, such as functional connectivity between brain regions, personality traits, or stressful life events, at baseline before treatment initiation. However, these moderators may resemble statelike qualities that fluctuate across time and contexts, rather than traits that remain stable over time. Research on precision treatment for depression has largely failed to examine the developmental trajectories and social or environmental contexts that may play a role in differential treatment response. Some factors may moderate differential treatment response at specific developmental stages or within certain environmental contexts, but this remains unknown. The episodic nature of depression itself also presents a challenge as response to specific treatments may vary between depressive episodes (Simon & Perlis, 2010). This is especially relevant given the high within-individual heterogeneity of depressive symptoms across months (Nemesure et al., 2024). Thus, response to treatment may be influenced by episode-level (i.e., time-varying) and patient-level (i.e., stable) characteristics.

Sociocultural Considerations

One of the largest limitations regarding work on precision treatment for depression is that the majority of results and conclusions drawn are based on White, Western populations (Henrich et al., 2010). Therefore, current biomarkers and clinical characteristics thought to be associated with differential treatment response for *depression* are really linked only to differential treatment response for *White, Western people with depression*. This is especially problematic given that minority and other underrepresented groups, largely neglected from research, may be at higher risk for specific forms of adversity (e.g., discrimination) that are known to increase the risk for psychopathology (Nazroo et al., 2020). When minority groups are involved in research, ethnicity is often treated as a covariate rather than acknowledged as a key factor shaping psychopathology (Dozois & Hayden, 2022). To better understand interactions between culture and psychopathology, culture should be directly studied rather than treated as a statistical control. For example, cultural differences among Indigenous Peoples in Canada are intertwined with genetic variations that inform precision treatment for psychopathology (Matheson et al., 2018). Bourque and Willox (2014) pointed to research that has found differences in gene expression and function across cultures. Moreover, epigenetics—the study of how life experiences can alter gene expression—should be considered in precision treatment, especially given that culture-specific traumas may exert transgenerational epigenetic effects (e.g., residential schools). These authors argued that genetic differences should be understood within the greater sociocultural context; although some epigenetic changes may increase the risk for psychopathology, genetic variations could also contribute to resilience in the face of adversity.

Relatedly, an understanding of precision treatment for depression is limited by a narrow focus on biological markers. Taking sociocultural context into account may be needed to advance our understanding of what treatment works best for whom. Ku et al. (2022), for instance, found that neighbourhood poverty was associated with reduced hippocampal volume in those at risk for psychosis but only when social engagement was low. Thus, social factors may be protective against neurobiological risk; however, research into precision treatment has failed to explore these relationships. As previously mentioned, precision psychiatry was modelled based on the successes of precision medicine as applied to the medical field, such as oncology (Hoeben et al., 2021). Although medical conditions often have identifiable biological causes, psychiatric conditions do not (Tabb & Lemoine, 2021). Mental disorders, such as depression, are likely to be the result of interactions among biological, psychological, and social factors (Borsboom et al., 2022); therefore, precision treatment for depression must take all levels of analysis into account. Indeed, social factors such as poverty, racism, and discrimination are more strongly related to mental health problems than many biological factors (Anglin et al., 2021; Wallack & Thornburg, 2016).

Conceptual Challenges

Especially given the significant costs and resources associated with precision treatment, one may ask: "Is precision treatment worth all the effort if every treatment is generally equal in effectiveness?" A meta-analysis comparing CBT, IPT, and nondirective supportive psychotherapy in depressed adults revealed that less than a fifth of the variance in patient outcomes was accounted for by specific treatment techniques (Cuijpers et al., 2012). Perhaps identifying optimal treatments is not necessary if most treatments tend to demonstrate similar outcomes. A related question one may ask is: "Should we expect moderators of specific treatment outcomes when treatments are so similar?" DeRubeis et al. (2014) suggested that precision treatment is most likely to work when treatments have different underlying mechanisms. For example, Eskildsen et al. (2020) examined 36 potential moderators of changes in well-being in patients randomized to either group CBT or group transdiagnostic CBT. Ultimately, these researchers failed to identify any specific moderators of treatment response, perhaps because both treatments shared similar mechanisms of change. Similar findings that CBT and IPT have considerable overlap in mechanisms and outcomes (Lorenzo-Luaces et al., 2015) may explain why few moderators of differential treatment response have been identified in the literature. However, investigations into differential treatment response

between CBT and antidepressants may have more merit given that they may work through different mechanisms. Canadian researchers have found differences in changes to brain regions following CBT versus antidepressant treatment, suggesting potential differences in mechanisms underlying their efficacy (Goldapple et al., 2004; Kennedy et al., 2007). Thus, researchers may consider whether treatment types have expected differences in mechanisms of change before searching for potential moderators of differential treatment response.

Questions, such as, "Should we expect moderators of specific treatment outcomes when treatments are so similar?" have motivated researchers to explore alternative treatment avenues. "Blanket" treatments that aim to reduce depression generally may not be effective universally given the between- and within-person heterogeneity of the disorder (Ingram et al., 1998, 2014; Nemesure et al., 2024). Research groups such as the Research Domain Criteria (RDoC; Insel et al., 2010) and the Unified Protocol (UP; Barlow et al., 2011) have moved past typical disorder-focused ways of understanding psychopathology and argue for a symptom-focused approach which models high comorbidity and heterogeneity seen across mental disorders. Specifically, the UP advocates for therapeutic techniques that target transdiagnostic symptoms rather than diagnoses. In the future, precision treatment for depression may work alongside the UP by guiding treatment selection based on an individual's unique symptom profile. However, given that symptoms can change dynamically throughout the course of depression (Nemesure et al., 2024), precision treatment may be better suited to select appropriate treatments based on an individual's specific set of modifiable vulnerability factors (i.e., causes not symptoms of the disorder; see Dozois & Dobson, 2023).

After decades of research, progress toward precision treatment for depression remains limited by practical and conceptual challenges. High costs and resources, difficulty in measuring and accounting for dynamic moderators, a narrow focus on biological factors, and the significant overlap between treatments all hinder the feasibility of a fully personalized approach. These limitations lead to questions about whether precision treatment is worth pursuing when most treatments for depression yield similar outcomes.

Future Directions of Precision Treatment for Depression

Despite its promise, precision treatment for depression remains limited by conceptual and practical challenges. Future research must address these limitations by integrating advances in biological, psychological, and social science with advanced technologies. Fortunately, recent developments in technology (e.g., machine learning and artificial intelligence), along with the growing recognition of depression as a heterogeneous disorder, have set the stage for precision treatment to *potentially* flourish. By leveraging these advancements and addressing existing barriers, researchers can arrive at a more comprehensive understanding of what treatment works best for whom and under what circumstances.

There are several steps researchers can take toward advancing precision treatment for depression. First, given that no single biological, clinical, or demographic moderator reliably or robustly predicts differential treatment outcomes for depression, researchers must integrate findings from various moderators across multiple levels of analysis. Toward PRecisiOn Medicine for the Prediction of Treatment response is a recent effort that aims to combine clinical, genomic, transcriptomic, and sex-related data to advance precision treatment for depression (Baune et al., 2024). This approach aims to create a clinically useful algorithm by integrating clinical data, such as depressive symptoms and history of childhood trauma, and biological data, as well as stratifying analyses according to sex, to account for sex-specific differences in depression. Second, researchers may reevaluate the *type* of treatments examined in precision treatment trials. Given that common factors explain much of the variance in treatment outcomes (Cuijpers et al., 2012), it may be worthwhile to investigate other aspects of treatment, such as high versus low levels of care. For example, Kessler (2018) argued that precision treatment could be used to determine who benefits from unguided self-help compared to face-to-face CBT; in this way, precision treatment could reduce treatment costs for those who would achieve comparable outcomes from more affordable and accessible interventions. Precision treatment may also be helpful in determining an individual's sequence of treatments. Increasingly, attention has been given to sequential treatment algorithms as a strategy to reduce residual symptoms after treatment by following one type of therapy with another (e.g., Fava, 1999). Indeed, following antidepressant medication with psychotherapy, either alone or in combination with medication, significantly reduces risk of relapse or recurrence of depression (Guidi & Fava, 2021). In the future, precision treatment could further optimize sequential treatment algorithms by identifying who would best benefit from a sequential approach and which treatment should precede another for a specific person. Importantly, the emergence of artificial intelligence (AI) may revolutionize precision treatment for depression. Perna et al. (2024) emphasized the importance of using large sample sizes and collecting data longitudinally across multiple depressive episodes to capture combinations of weak predictors rather than single, powerful ones. The authors contend that these needs can be fulfilled by recent technological innovations, such as electronic databases capable of storing big data, wearable devices that collect data in real time, and machine learning methods that can recognize complex patterns and generate predictive models, surpassing human capabilities. Last, Gómez-Carrillo et al. (2023) recommended that precision treatment for depression can move forward by taking an ecosocial approach. By considering the priorities and needs of those with lived experience, understanding individuals within their social contexts, promoting interdisciplinary collaboration, and ensuring representative and culturally diverse samples, the question of what works best for whom can be answered holistically.

Clinical Recommendations

Although precision treatment for depression remains an evolving field, clinicians are not without tools to enhance treatment outcomes. Personalized treatment does exist in the sense that targeted interventions are designed to be effective for particular disorders. Thus, clinicians should select treatments with a strong evidence base for a given disorder. For example, CBT, behavioural activation, and IPT are evidenced-based treatments for depression (Hollon & Ponniah, 2010; Lam et al., 2024). However, because nearly half of individuals with one mental disorder will meet diagnostic criteria for another (Kessler et al., 2005), matching treatments to disorders can be complicated. Clinicians should also recognize that treatments may work differently for patients with attributes that are unrelated to their diagnosis. This idea is supported by a large body of literature on

Aptitude × Treatment interactions (Constantine et al., 2021; Cronbach & Snow, 1977) which supports certain predictors of treatment response. For example, individuals with depression and a comorbid personality disorder may respond better to medication (Bagby et al., 2008; Fournier et al., 2009), whereas individuals with depression and a history of trauma or stressful life events may favour psychotherapy (Fournier et al., 2009; Nemeroff et al., 2003).

Following what Meehl (1954) argued over half a century ago, clinicians should consult empirical evidence, rather than solely exercise clinical judgement, when selecting appropriate treatments for specific disorders. Although empirical evidence on precision treatment for depression is fraught with limitations, empirical evidence on treatment efficacy, rather than clinical judgement, remains the best strategy for treatment selection. Evidence-based treatments are emphasized in clinical training but are not always used in clinical practice (Dozois, 2013). To improve treatment outcomes, clinicians need to place trust in science and resolve any misconceptions they have about evidence-based care (Lilienfeld et al., 2013). Although using clinical judgement is an *intuitive* approach, clinicians, like all humans, have innate biases (e.g., confirmation bias) that interfere with sound decision making (Cohen et al., 2021; Dozois, 2013; Grove & Meehl, 1996; Meehl, 1954). Currently, there is no way to reliably and robustly predict what treatment will work best for whom based on their individual characteristics. Thus, until precise methods prove to be clinically useful, clinicians should select treatment based on general patterns of treatment efficacy. Clinicians should consider the hierarchy of evidence when evaluating treatment options and prioritize interventions that are supported by research findings from systematic knowledge syntheses (e.g., systematic reviews and meta-analyses) published in peer-reviewed journals (Dozois et al., 2014). If systematic knowledge syntheses are not available, clinicians should refer to primary research studies with high internal and external validity before relying on professional opinion or prior experience. Additionally, the Canadian Network for Mood and Anxiety Treatments' clinical guidelines on the management of major depressive disorder in adults (Lam et al., 2024) offer comprehensive, evidence-based recommendations for the treatment of depression and should be considered an essential resource.

Importantly, clinicians must acknowledge that depression is a heterogeneous condition. Thus, treatment that works for one patient with depression may not work for another. Even when treatment selection is grounded in strong empirical evidence, many patients do not respond to their first course of treatment (Hollon et al., 2002). Therefore, clinicians should routinely monitor patients' symptoms using validated assessments (Dozois et al., 2014). In this way, outcome monitoring offers an empirical way for clinicians to track patients' progress and decide whether treatment should be continued, changed, or terminated. The Canadian Psychological Association's (2018) Task Force on Outcome Monitoring in Psychotherapy (also see Tasca et al., 2019) emphasizes the importance of integrating outcome monitoring into practice, highlighting that the consistent assessment of patient outcomes can improve treatment efficacy. Numerous psychometrically sound measures are available to monitor depressive symptoms throughout the course of treatment (see Dozois et al., 2020). For instance, both clinician-rated indices, such as the HAM-D (Hamilton, 1960) and Montgomery–Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979), and self-report measures, such as the Beck Depression Inventory-II (Beck et al., 1996), the Depression Anxiety Stress Scales (Lovibond & Lovibond, 1995), and the Patient Health Questionnaire (Kroenke et al., 1999), can assess patient progress by measuring changes in symptoms during the course of treatment. Importantly, the Outcome Questionnaire (OQ-System; Lambert & Harmon, 2018; Lambert et al., 2013) is an evidence-based transdiagnostic tool that measures patient progress to systematically predict treatment failure; in this way, clinicians can better assess when adjustments to the treatment plan should be made. When a patient is not responding to treatment or deteriorating, clinicians should be prepared to modify their treatment approach. Indeed, switching, combining, or sequencing treatment modalities may be effective for nonresponders (Cuijpers et al., 2020; Guidi & Fava, 2021).[1] As treatment modalities are often siloed (e.g., Canadian psychologists cannot currently prescribe antidepressants), modifications to the treatment plan may warrant referrals to other clinicians or health care providers. In these cases, the use of multidisciplinary teams can streamline this process. A unified team of health care professionals with distinct expertise in their field may be best suited to treat a heterogeneous disorder, such as depression, that has biological, psychological, and social underpinnings. Thus, addressing the heterogeneity of depression may require outcome monitoring and a coordinated approach to bridge gaps between treatment modalities.

At a time when precision treatment for depression has yet to be successfully implemented into clinical practice, Simon and Perlis (2010) recommended that clinicians be honest with their patients about treatment selection. For example, clinicians can explain, "Although we currently have no way to predict exactly which treatment will work best for you, we have several treatment options that are similarly effective. If one does not work, we can find another that may work for you." In this way, clinicians can instill hope and trust in patients, strengthening the therapeutic alliance, while accurately representing what is currently possible. Although precision treatment for depression remains an aspirational goal, clinicians can improve their practice in the meantime by remaining evidence-based, monitoring patients' outcomes in treatment, and ensuring that they are both ready and able to adjust the treatment plan if needed.

Conclusion

Overall, precision treatment for depression represents a *theoretically* promising, but *realistically* limited approach. Decades of research into genetic, neurological, biological, clinical, and demographic factors have yet to lead to any clinically useful advancements in predicting differential responses to treatment for depression. However, recent developments, especially in technology, combined with holistic frameworks that integrate biopsychosocial factors, may pave the way for precision treatment for depression to be fully realized. Ultimately, much work must be done before we can precisely understand "what treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances?" (Paul, 1967, p. 111).

[1] Switching psychotherapies may be effective, but no strong evidence suggests that switching antidepressant medication is any more effective than continued use (Bschor et al., 2018).

Résumé

La dépression, l'une des principales causes d'invalidité dans le monde, peut être traitée avec succès par plusieurs interventions fondées sur des données probantes. Cependant, les réponses individuelles à ces traitements varient considérablement et de nombreuses personnes suivent plusieurs thérapies avant de trouver celle qui leur convient le mieux. Le traitement de précision de la dépression vise à relever ces défis en identifiant les traitements efficaces en fonction des caractéristiques individuelles. Ce faisant, le traitement de précision pourrait réduire les prescriptions par essais et erreurs, raccourcir le délai de rémission et alléger le fardeau mondial de la dépression. Cependant, malgré des décennies de recherche, le traitement de précision n'a pas encore été pleinement concrétisé pour la dépression, et son utilité clinique demeure limitée. Cet article présente des exemples d'initiatives récentes et pertinentes visant à identifier les facteurs prédictifs de la réponse différentielle au traitement et soulève certaines questions méthodologiques, conceptuelles et pratiques liées à la mise en œuvre d'un traitement de précision pour la dépression. Les orientations futures et les implications cliniques pour faire progresser les approches personnalisées du traitement de la dépression sont également examinées.

Mots-clés : médecine de précision, psychiatrie de précision, médecine personnalisée, traitement personnalisé, dépression

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